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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076401 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/09378

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/278,837 26 March 2001 (26.03.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076401 A2

(54) Title: METHOD OF ATTENUATING REACTIONS TO SKIN IRRITANTS

(57) Abstract: The present invention is directed to a method of inhibiting CD1d activation by administering a composition containing a moiety that blocks CD1d activation. Compositions of the invention are useful for the attenuation of CD1d-restricted immune responses, including treatment of skin disorders due to hyperactive immune responses (e.g., contact hypersensitivity), for systemic administration to attenuate ongoing immune responses, and to provide hypoallergenic cosmetic products including pharmaceutical, cosmetic, and skin care compositions. Preferably, these compositions are in a form intended for topical administration.

The reactions include typical allergic dermatitis, including contact dermatitis and atopic dermatitis, as well as irritant dermatitis.

Contact dermatitis is an inflammation of the skin, which occurs when the skin comes in contact with substances that the skin is sensitive or allergic to. The reaction usually appears within 24-48 hours after exposure to the allergen. Common symptoms include redness, itching and swelling. Sometimes blistering and weeping of the skin also develop. The clinical symptoms of contact dermatitis can include acute eczema accompanied by erythema, edema, papula, vesicle, erosion, and itching. Repeated exposure to an irritant can lead to the development of eczema accompanying lichenification and infiltration. Allergic contact dermatitis can appear after initial or prolonged exposure to an irritant. Contact dermatitis includes irritant dermatitis, phototoxic dermatitis, allergic dermatitis, photoallergic dermatitis, contact urticaria, systemic contact-type dermatitis and the like.

A wide range of agents can cause allergic contact dermatitis including for example, metals (e.g. nickel, chromium, cobalt), fragrances, chemicals, cosmetics, textiles, pesticides, plastics, and pollen (see, for example, R. J. G. Rycroft et al. "Textbook of Contact Dermatitis").

Therapeutic agents such as drugs may also cause allergic contact dermatitis, particularly when administered transdermally. It is well known that many drugs, e.g., topical ointments, including some currently marketed in the United States (e.g. clonidine) sensitize the skin when used.

Skin sensitization may be produced not only by transdermally delivered drugs, but also by a non-sensitizing drug combined with skin sensitizing permeation enhancers, or a combination of a sensitizing drug and a sensitizing permeation

Certain irritants may cause both allergic and non-allergic contact dermatitis. For example, latex. Latex refers to a type of plastic made from the milky sap of the rubber tree, and contains many proteins which can cause allergic reactions in sensitive individuals. Symptoms can range from watery eyes, hives, rash, swelling, wheezing and in severe cases, anaphylaxis. These responses can occur when latex items touch the skin; the mucous membranes (including the mouth, bladder, genitals, or rectum), and open wounds or bloodstream (especially during surgery). Anybody can develop latex sensitivity. People at increased risk for developing latex allergy include workers with ongoing latex contact (like health care workers), persons with many environmental allergies (hay fever), and those with spina bifida. Latex is found in a wide array of common products, including, for example: gloves, balloons, band-aids, tourniquets, bandages, catheters, rubber bands, IV, other tubing (ex. stethoscopes), art supplies, pacifiers, bottle nipples, diapers, condoms/diaphragms, elastic, chewing gum, carpeting, hand grips of bicycles and motorcycles, shoe soles, auto tires, swimming goggles and equipment.

The more common reaction to latex products is not allergic, but rather, irritant contact dermatitis, which can cause dry, itchy, irritated areas on the skin, usually the hands. Skin reactions include a rash that usually begins 24 to 48 hours after contact. It may progress to oozing blisters or spread away from area touched by latex. Latex allergy (immediate hypersensitivity) is a more serious reaction. Certain proteins in latex cause an allergic reaction. The amount of exposure needed to cause symptoms is not known. Very low levels of exposure can trigger allergic reactions in some people, while having no affect to most people. Reactions usually begin within minutes of exposure to latex, but can occur hours later and have a variety of symptoms. Mild

Individual topical corticosteroid preparations vary in anti-inflammatory potency and clinical efficacy.

Though some steroids, particularly mid- to high-potency steroids, are efficacious in chronic dermatoses, long term use of steroids is associated with serious local side effects. These include skin atrophy (thinning, telangiectasia, striae) and a prompt rebound flare when the steroid is stopped. Treatment of large areas of skin and use of occlusive dressings can also increase the potential for adverse effects. This is especially the case in children.

Examples of anti-histamine agents include diphenhydramine hydrochloride, mequitazine, promethazine hydrochloride, and chlorpheniramine maleate anti-histamines have been used mainly to reduce itchiness. Anti-allergic agents include tranilast, ketotifen fumarate, oxatomide, and azelastine hydrochloride. In general, conventional so-called antiallergic agents are either ineffective or fail to show satisfactory therapeutic effects on contact dermatitis and atopic dermatitis.

Accordingly, there is a need for a treatment for skin reactions including allergic dermatitis (contact dermatitis and atopic dermatitis), as well as irritant dermatitis.

The pathophysiologic mechanisms involved in the above-described skin disorders and the evolution of such inflammatory processes are poorly understood. There are numerous skin conditions characterized by increased T cell activation and abnormal antigen presentation in the dermis and epidermis. Thus, there has been speculation that skin cells are important in the generation of a cutaneous inflammatory response (Kupper, "Immune and Inflammatory Processes in Cutaneous Tissues", J. Clin. Invest., 86, pp. 1783-89 (1990)).

Another preferred group of compositions includes glycolipid antagonists that bind CD1d without activating NK T cells. Preferred glycolipids include ceramide, αMan Cer, and βGal Cer.

Another preferred group of compositions includes phosphatidyl inositol.

This method of attenuating CD1d activation can be used for treatment of conditions associated with activation of CD1d-restricted NK T cells. Preferred conditions include skin disorders due to hyperactive CD1d-restricted T cell responses and other disorders associated with ongoing CD1d-restricted immune responses.

Such CD1d associated skin disorders include contact dermatitis and further eczematous dermatitises, atopical dermatitis, seborrheic dermatitis, psoriasis, Lichen planus, Pemphigus, bullous Pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinphilias, Lupus erythematosus, and Alopecia areata.

A preferred embodiment of the invention is directed to the treatment of contact hypersensitivity.

Another embodiment of the invention provides hypoallergenic cosmetic products.

Another embodiment of the invention is directed to compositions that can be used prophylactically to prevent a reaction before one encounters the irritant. For example, a composition to use before weeding.

One preferred embodiment of the invention provides preventing or treating skin sensitization produced by topical administration of therapeutic drugs.

the right ear was challenged with 0.5% oxazolone, 10 μl on each side or carrier only. The hapten specific increase in ear thickness at 24 hours was determined using a micrometer.

Figure 3 is a graph showing that topical DPPE-PEG (a CD1d-binding lipid) inhibits oxazolone-induced contact hypersensitivity. Mice at least seven weeks of age were sensitized epicutaneously on day 0 with 70 l of 4% 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (oxazolone, Sigma) in acetone/olive oil (4/1) with or without DPPE-PEG (100 mg/ml) and challenged five days later on the ear with 20 l of 0.5% oxazolone or carrier only. The hapten-specific increase in ear thickness at 24 hours was determined with a micrometer.

Figure 4A is a dose response curve showing that topical administration of DPPE-PEG inhibits oxazolone-induced contact hypersensitivity in a dose dependent fashion. Mice at least seven weeks of age were sensitized epicutaneously on day 0 with 70 l of 4% oxazolone in acetone/olive oil (4/1) with DPPE-PEG in a series of increasing dosage, ranging from 0 to 100 mg/ml. 5 days later the right ear was challenged with 0.5% oxazolone, 10 l on each side or carrier only. The hapten specific increase in ear thickness at 24 hours was determined using a micrometer. Figure 4B is a graph showing topical administration of DPPE-PEG inhibits oxazolone-induced contact hypersensitivity both during recall and priming. Mice at least seven weeks of age were sensitized epicutaneously on day 0 with 70 l of 4% oxazolone in acetone/olive oil (4/1) with or without DPPE-PEG. 5 days later the right ear was challenged with 0.5% oxazolone, 10 l on each side or carrier only. One group that was primed with oxazolone only was challenged with a mixture of

suffering from an activated CD1d associated disorder such as a skin disorder by administering an effective amount of CD1d specific antagonist.

Such compounds include antagonists that bind CD1d and inhibit NK T cell activation, antagonists that block CD1d-specific receptors such as on NK T cells, decoys that prevent CD1d binding to the CD1d specific receptor, and the like.

Experiments in human models have revealed that CD1d-restricted CD161+ T cells specifically target myeloid dendritic (DC1) cells. DC1 dendritic cells are integral to the genesis of Th1 immune responses. Accordingly, their susceptibility to lysis by CD1d-restricted CD161+ T cells may be part of a negative feedback loop in cell-mediated immune responses.

We tested dendritic cell function in CD1d null and wild type mice. The CD1d mull mice had impaired priming responses in mixed lymphocyte reactions, to tumor vaccinations, and in skin contact hypersensitivity (see Figure 1). In addition, contact hypersensitivity could be blocked by the cutaneous addition of lipid ligands know to bind CD1d but not activate NK T cells (see Figure 2).

Accordingly, one can readily determine whether a compound inhibits activation of CD1d by looking at activation of CD1d-restricted NK T cells *in vitro* using standard assays such as described herein. For example, the proliferation of NK T cells is indicative of their activation by binding to CD1d-expressing cells. Proliferation can be measured, for example, by determining the incorporation of [^{3}H] thymidine into Vα14 NK T cells (Kawano et al., *Science* 278:1626-29 (1997)). Other *in vitro* assays include the induction of cytokine production.

presented by CD1d is -galactosylceramide (Kawano et al., 1997). Thus, D1d antagonists can include glycolipids such as monoglycosylated ceramides and diglycosylated ceramides (Kawano et al., 1997).

Examples of monoglycosylated ceramides and diglycosylated ceramides which bind CD1d but do not activate NK T cells can include ceramides with inner sugar groups at the β-anomer position (such as Galα1-4Glcβ1-1'Cer), an axial configuration of the 2-hydroxyl group (such as α-ManCer), derivatives lacking the 3- and 4-hydroxyl groups on the phytosphingosine of α-GalCer (such as 3,4-deoxy α-GalCer), and ceramides with fatty acyl chain with less than C_{26}, and a sphingosine base less than C_{18}. Glycolipid antagonists can also be coupled to a conjugate such as biotin or a poly(alkylene oxide), for example PEG.

Other CD1d glycolipid antagonists include highly glycosylated sphingolipids, also known as gangliosides. Ganglioside antagonists include GM1 and GD1a (Naidenko et al., 1997). The antagonists can be coupled to a conjugate such as a biotin or poly (alkylene oxide).

Preferred examples of CD1d-specific lipid antagonists include but are not limited to: DPPE-PEG, phosphatidyl inositol, ceramide, α-ManCer, β-GalCer, Galα1-4Glcβ1-1'Cer, and 13,4-deoxy α-GalCer, GM1, and GD1a.

Other antagonists can include antibodies that specifically bind to CD1d and in doing so prevent CD1d from binding to a CD1d specific receptor. Single chain antibodies and humanized monoclonal antibodies are preferred. Alternatively, one can use molecules that block the CD1d-specific receptor. For example, a molecule. Alternatively, one can modify the lipids that activate CD1d binding by capping the

attenuation of CD1d activation, such as attenuation of the CD1d-restricted NK T cell response, would be desirable. Preferred embodiments of the invention include topical administration to treat skin disorders due to hyperactive immune responses (e.g., contact hypersensitivity) and systemic administration. Prophylactic use to attenuate immune responses. For example, to avoid reactions to certain plants such as poison ivy, poison oak, etc. when you are going to be in an area where exposure to such a substance is likely, for example, if you are going to be in the woods, gardening, etc.

Systemic administration is preferred in any individual for which activation of NKT cells would be adverse.

Certain women have a problem with spontaneous abortion which appears to be associated with high levels of CD1d. These individuals could use the present compositions before trying to conceive, preferably using systemic administration.

Certain individuals with autoimmune diseases have complications associated in part with CD1d activation. These compositions can be used with such individuals.

One problem with allergic or irritant caused itching is that the scratching can in fact result in further irritation that causes rashes and irritation long after the initial stimulus is gone. This is a particular problem with non-human animals. These compositions can be used to attenuate, treat or present such conditions. Another preferred embodiment includes the composition in hypoallergenic cosmetic products.

In one embodiment of the invention, a locally administrable topical pharmaceutical composition is provided for the prevention or treatment of skin conditions associated with CD1d-restricted T cell responses. Skin conditions include, but are not limited to, contact dermatitis and further eczematous dermatitises, atopical

scaling, skin lesions containing infiltrates of neutrophils, lymphocytes, and monocytes. The compositions and methods of the present invention can be used to treat any form of psoriasis, including cutaneous, mucosal, ungual, and even psoriatic rheumatism. Compositions and methods of the present invention can be used to treat localized and generalized psoriasis.

One preferred embodiment of the invention provides prophylactic treatment to minimize skin sensitization produced by topical administration of therapeutic drugs. In another embodiment, the composition can be administered with the therapeutic drug or cosmetic. In still another embodiment, the composition is used for treatment after the reaction has occurred.

Another embodiment of the invention provides systemic administration of compositions to attenuate ongoing CD1d-restricted immune responses. This embodiment is preferable for any individual for whom activation of NKT cells would be adverse. Systemic conditions can include certain high risk spontaneously aborting pregnancies. It can also be used with autoimmune diseases such as lupus.

In another embodiment of the invention, a locally administrable topical cosmetic composition is provided, for example to provide hypoallergenic products.

The compositions of the present invention include those suitable for topical and systemic administration including oral, rectal, intravaginal, nasal, ophthalmic or parenteral administration, all of which may be used as routes of administration using the materials of the present invention. A preferred route of administration is topical. The topical composition may be in the form of a pharmaceutical but it does not have to be. For example, it can be a cosmetic.

Practice of Pharmacy, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oleaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (OW) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight (Remington: The Science and Practice of Pharmacy).

Lotions are preparations to be applied to the skin surface without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid composition. It is generally necessary that the insoluble matter in a lotion be finely divided. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, e.g., methylcellulose or sodium carboxymethyl-cellulose, or the like. A particularly preferred lotion formulation for use in conjunction with the present invention contains propylene glycol mixed with a hydrophilic petrolatum such as that which may be

Other agents may also be added, such as antimicrobial agents, antifungal agents, antibiotics and anti-inflammatory agents such as steroids.

In the preferred topical formulations of the invention, the active agent is present in an amount which is generally less than 10% by weight of the total composition, preferably less than about 1% by weight, and most preferably less than about 0.1% by weight.

The topical compositions of the invention may also be delivered to the skin using a time-release mechanism. For example, "transdermal"-type patches, wherein the CD1d activation-blocking composition is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Examples of suitable skin contact adhesive materials include, but are not limited to, polyethylenes, polysiloxanes, polyisobutylenes, polyacrylates, polyurethanes, and the like. The particular polymeric adhesive selected will depend on the particular drug, vehicle, etc., i.e., the adhesive must be compatible with all components of the drug-containing composition. In an alternative embodiment, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form.

number of components. In some cases, the blocking composition may be delivered "neat," i.e., in the absence of additional liquid. In most cases, however, the composition will be dissolved, dispersed or suspended in a suitable pharmaceutically acceptable vehicle, typically a solvent or gel. Other components which may be present include preservatives, stabilizers, surfactants, and the like.

Preferably, the topical formulations and the laminated delivery systems also contain a skin permeation enhancer. A skin permeation enhancer can be co-administered. Suitable enhancers are well know in the art and include, for example, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C_{10} MSO), C_2 -C_6 alkanediols, and the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone.RTM. from Whitby Research Incorporated, Richmond, Va.), alcohols, and the like.

The ointments, pastes, creams and gels also may contain excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

The topical compositions according to this invention may also include one or more preservatives or bacteriostatic agents, e.g., methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, and the like. The topical

The percentage of the antimicrobial agents in the composition is about 0.01 wt. % to about 10 wt. %, and preferably, about 0.01 wt. % to about 2 wt. %.

In one embodiment such as where a latex condom or diaphragm is to be used, the CD1d activation block compositions can be included in ointments, foams, and creams that can be used during sex. For example, they can be administered preferably prior to or just after sexual contact such as intercourse. One preferred composition would be a vaginal foam, including a spermicide, containing one of the compounds.

The topical compositions and drug delivery systems of the invention can be used in the prevention or treatment of the skin conditions identified above. When used in a preventive (prophylactic) method, susceptible skin can be treated prior to exposure or just after exposure but any visible lesions on areas known to be susceptible to such lesions are observed. In treating skin conditions, it will be recognized by those skilled in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular individual undergoing treatment, and that such optimums can be determined by conventional techniques. It will also be appreciated by one skilled in the art that the optimal dosing regimen, i.e., the number of doses can be ascertained using conventional course of treatment determination tests. Generally, a dosing regimen will involve administration of the selected topical formulation at least once daily, and preferably one to four times daily, until the symptoms have subsided.

Systemic administration of a composition may be by oral, parenteral, sublingual, rectal such as suppository or enteral administration, or by pulmonary absorption. Parenteral administration may be by intravenous injection, subcutaneous

modified to withstand very low pH conditions and resist the enzymes of the gastric mucosa such as by neutralizing an ionic group, by covalently bonding an ionic interaction, or by stabilizing or removing a disulfide bond or other relatively labile bond.

Treatments to the patient may be therapeutic or prophylactic. Therapeutic treatment involves administration of one or more compositions of the invention to a patient suffering from one or more symptoms of the disorder. Relief and even partial relief from one or more symptoms can correspond to an increased life span or simply an increased quality of life. Further, treatments that alleviate a pathological symptom can allow for other treatments to be administered.

The term "compatible", as used herein, means that the components of the compositions are capable of being commingled with the CD1d blocking agents of the present invention, and with each other, in a manner such that does not substantially impair the desired efficacy.

Doses of the pharmaceutical compositions of the invention will vary depending on the subject and upon the particular route of administration used. Dosages can range from 0.1 to 100,000 μg/kg per day, more preferably 1 to 10,000 μg/kg. By way of an example only, an overall dose range of from about, for example, 1 microgram to about 300 micrograms might be used for human use. This dose can be delivered at periodic intervals based upon the composition.

with 20 µl of 0.5% oxazolone or carrier only on the left ear. The hapten-specific increase in ear thickness at 24 hours was determined with a micrometer. For experiments using DPPE-PEG, 4% oxazolone in acetone/olive oil (4/1) solutions with or without DPPE-PEG (in dosages ranging from 5mg/ml to 100 mg/ml) were applied. Finally, a mixture off 0.5% oxazolone and 50mg/ml DPPE-PEG was used for the inhibition of oxazalone recall.

Analysis of invariant Vα14Jα281 TCR frequency. Total RNA was isolated from spleens of individual mice using TRIZOL (Gibro BRL, Grand Island, New York) according to the manufacturer's recommendations. First-strand cDNA synthesis was performed using oligo(dT) as a primer for reverse transcription of 2 µgof total RNA in a 50 µl reaction mixture using MMLV-RT (Life Technologies, GIBCO-BRL, Gaithersgurg, MA). Quantitative analysis of Vα14Jα281 T cell frequency was done using multiplex RT-PCR by comparing the intensity of the TCR α–chain CDR3 band with the invariant INKT cell specific band, as previously described (29).

Treatment protocols

Mice received a series of 5 intraperitoneal injections of either 2 µg of αManCer (2 µg i.p. diluted in a solution of phosphate buffered saline and 0.5% Tween-20 every other day, starting 3 days prior to skin sensitization and continuing through to re-challenge.

Statistical analysis

with the protypic CD1d-dependent glycolipid agonist α-GalCer or antagonist α-ManCer, a glycolipid that is known to bind CD1d but fails to activate iNKT cells, would modulate CSH responses. Mice were treated with the α-GalCer or α-ManCer by i.p. injections administered prior to and during the sensitization phase with oxazolone. Pretreatment of mice with α-ManCer inhibited the CSH response by 50% when compared to the control group (Figure 2). Conversely, administration of α-GalCer did not alter the CSH response to oxazolone. Thus, CHS responses were not augmented by iNKT cell activation, but could be significantly inhibited by systemic treatment with CD1d antagonists previously demonstrated not to activate iNKT cells in vivo and in vitro.

Topical DPPE-PEG (a CD1d-binding lipid) inhibits oxazolone-induced contact hypersensitivity (Figure 3). Mice were sensitized epicutaneously on day 0 with oxazolone with or without DPPE-PEG (100 mg/ml) and challenged five days later on the ear with oxazolone or carrier only, as described above. The hapten-specific increase in ear thickness at 24 hours was determined with a micrometer.

Topical administration of iNKT antogonist lipids inhibited the generation of CHS. Increasing doses of DPPE-PEG inhibit oxazolone-induced hypersensitivity in a dose-dependent manner, as shown in Figure 4A. We evaluated whether administration of CD1d antagonists could be used topically to block the generation of CSH responses. Since a synthetically modified lipid, DPPE-PEG, was recently demonstrated to be a significantly more soluble and effective competitor of α-GalCer presentation than α-ManCer and was available in pharmacologic quantities, (22) this reagent was chosen for use as a topical inhibitor of CSH. In control experiments systemic administration of DPPE-PEG or PEG-ceramide inhibited CHS as effectively

the ability of DPPE-PEG to inhibit CSH. Therefore, DPPE-PEG was an effective inhibitor of oxazolone-induced CSH in a MHC-independent fashion and in all strains tested.

CSH reactions were inhibited in mice deficient in iNKT cells directly confirming an important role for iNKT cells in CSH. Furthermore, CHS was specifically inhibited in those mice that were treated with CD1d-binding antagonists. Thus, blockade of the CD1d system could be used to treat ACD in an antigen- and MHC-independent fashion.

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All references described herein are incorporated herein by reference.

8. The method of claim 7, wherein the CD1d-restricted NK T cells responses are associated with skin disorders due to hyperactive CD1d-restricted T cell responses and other disorders associated with ongoing CD1d-restricted immune responses.

9. The method of claim 8, wherein the skin disorders include contact dermatitis and further eczematous dermatitises, atopical dermatitis, seborrheic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinphilias, Lupus erythematosus, and Alopecia areata.

10. The method of claim 7, wherein the CD1d-restricted NK T cells responses are associated with psoriasis.

11. The method of claim 8, wherein the skin disorder is contact dermatitis.

12. The method of claim 7, wherein the composition is present in a pharmaceutical composition, moisturizing composition or a cosmetic composition.

13. The composition of claim 7, wherein the agent is a phospholipid that binds CD1d without activating NK T cells.

14. The composition of claim 13, wherein the phospholipid is selected from the group consisting of 1,2-Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine (DPPE) and 1,2-Dipalmitoyl-sn-Glycero-3-Phosphoethanolamine-N-[Poly(ethylene glycol) 2000] (DPPE-PEG).

15. The composition of claim 7, wherein the agent is a glycolipid.

16. The composition of claim 15, wherein the glycolipid is selected from the group consisting of ceramide, αMan Cer, and βGal Cer.

atopical dermatitis, seborrheic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinphilias, Lupus erythematosus, psoriasis and Alopecia areata.

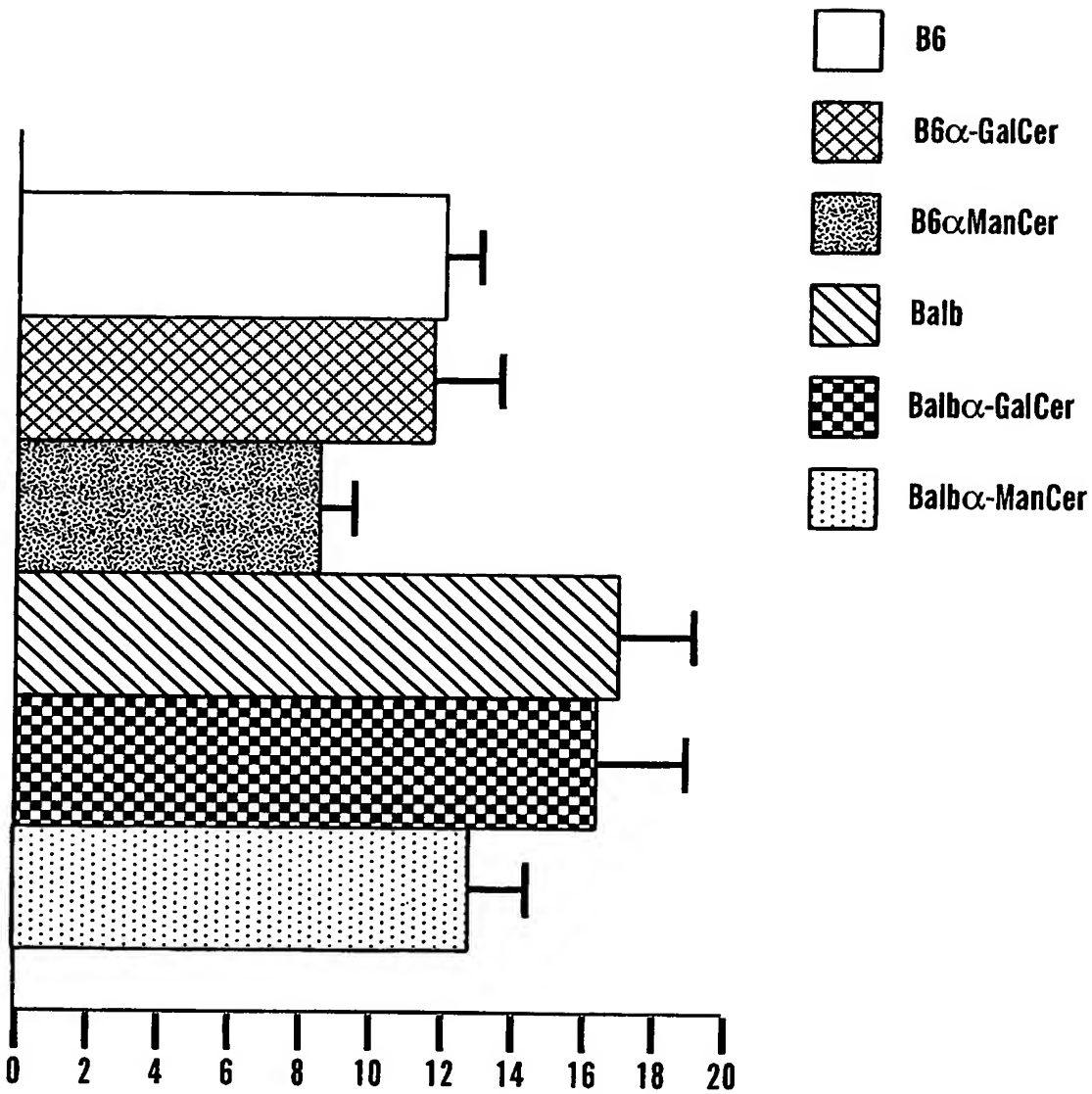

FIG. 2

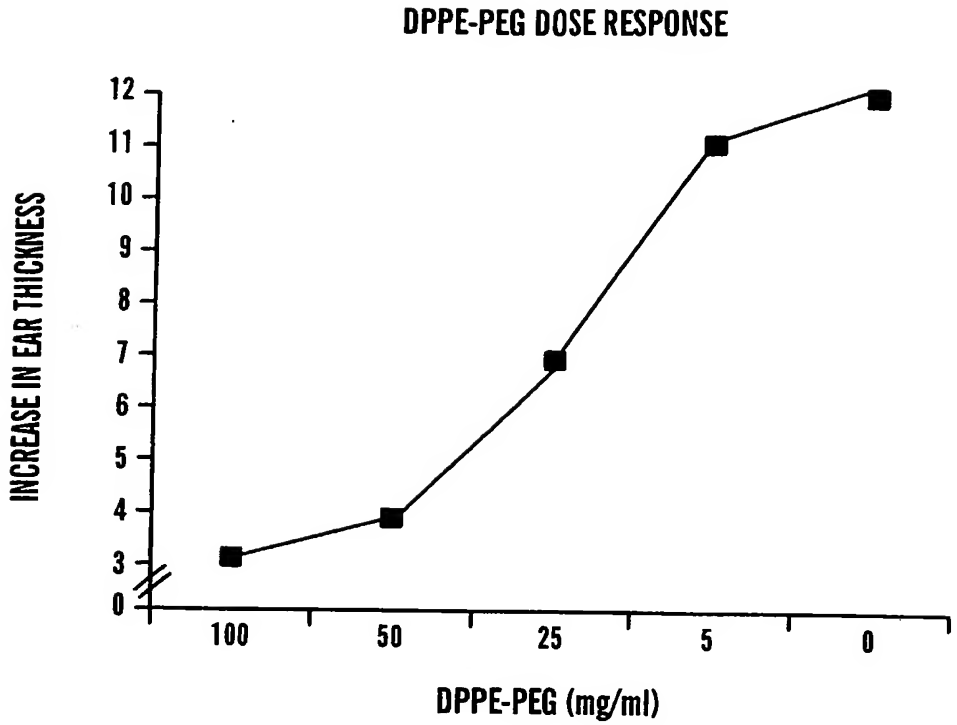

FIG. 4A

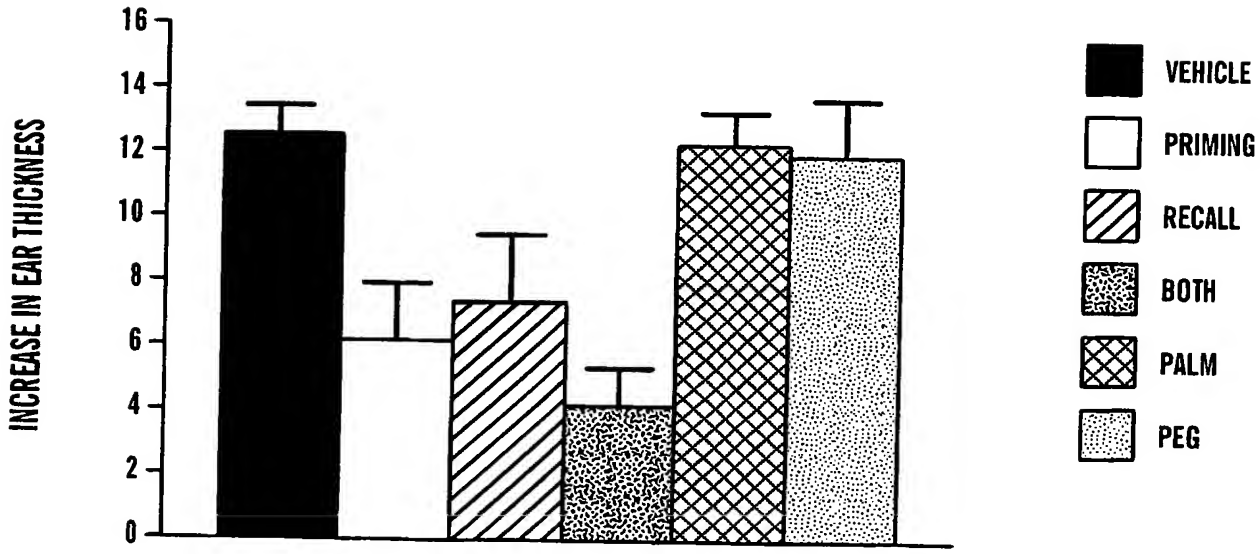

FIG. 4B

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076401 A3

(51) International Patent Classification[7]: A61K 31/66, 31/70

(21) International Application Number: PCT/US02/09378

(22) International Filing Date: 26 March 2002 (26.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/278,837 26 March 2001 (26.03.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
27 February 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/076401 A3

(54) Title: METHOD OF ATTENUATING REACTIONS TO SKIN IRRITANTS

(57) Abstract: The present invention is directed to a method of inhibiting CD1d activation by administering a composition containing a moiety that blocks CD1d activation. Compositions of the invention are useful for the attenuation of CD1d-restricted immune responses, including treatment of skin disorders due to hyperactive immune responses (e.g., contact hypersensitivity), for systemic administration to attenuate ongoing immune responses, and to provide hypoallergenic cosmetic products including pharmaceutical, cosmetic, and skin care compositions. Preferably, these compositions are in a form intended for topical administration.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/09378

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 13-16
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

No meaningful search could be carried out because these claims are directed to compositions while they depend from a claim which defines a method.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.